MLH1, *MSH2*, *MSH6*, *PMS2*, and/or *EPCAM* Sequencing and/or Deletion/Duplication Analysis

I. Lynch syndrome panels, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and/or *EPCAM* sequencing and/or duplication analysis for Lynch syndrome/HNPCC is considered **medically necessary** when:

A. The member has a tumor that shows evidence of mismatch repair (MMR) deficiency (either by microsatellite instability (MSI) or loss of MMR protein expression), **OR**

B. The member has a diagnosis of a Lynch syndrome-related cancer (colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma), **AND** any of the following:

1. Diagnosed before age 50, **OR**
2. Diagnosed at any age with an additional Lynch syndrome-related cancer, **OR**
3. Diagnosed at any age with one or more first- or second-degree relatives diagnosed before age 50 with a Lynch syndrome-related cancer, **OR**
4. Diagnosed at any age with two or more first- or second-degree relatives diagnosed at any age with a Lynch syndrome-related cancer, **OR**

C. The member has a family history of **any** of the following:

1. One or more first-degree relatives diagnosed with colorectal or endometrial cancer before age 50, **OR**
2. One or more first- or second-degree relatives diagnosed with colorectal or endometrial cancer and an additional Lynch syndrome-related cancer, **OR**
3. Two or more first- or second-degree relatives on the same side of the family diagnosed with a Lynch syndrome-related cancer, one of whom was diagnosed before age 50, **OR**

4. Three or more first- or second-degree relatives on the same side of the family diagnosed with a Lynch syndrome-related cancer, **OR**

D. The member has a 5% or greater risk of having Lynch syndrome based on one of the following variant prediction models: MMRpro, PREMM5, MMRpredict, **OR**

E. The member has a personal history of colorectal and/or endometrial cancer with a PREMM5 score of 2.5% or greater.

II. Lynch syndrome panel, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and/or *EPCAM* sequencing and/or duplication analysis for Lynch syndrome/HNPCC is considered **investigational** for all other indications.

III. *MLH1, MSH2, MSH6, PMS2* and *EPCAM* mRNA sequencing analysis for the interpretation of variants of unknown significance is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance, or follow up testing without proven utility.

RATIONALE AND REFERENCES

MLH1, MSH2, MSH6, PMS2, and/or *EPCAM* Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (1.2025)

This guideline outlines testing criteria for the evaluation of Lynch syndrome. These criteria include:

- An individual with a Lynch-syndrome (LS)-related cancer (colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, and small intestine, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas) and any of the following:
  - Diagnosed younger than 50 years
  - A synchronous or metachronous LS-related cancer regardless of age
  - 1 first-degree or second-degree relative with an LS-related cancer diagnosed younger than 50 years
  - 2 or more first-degree or second-degree relatives with an LS-related

cancer regardless of age
- Family history of any of the following
    - At least 1 first-degree relative with a colorectal or endometrial cancer diagnosed younger than 50 years
    - At least 1 first- or second-degree relative with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer regardless of age
    - 2 or more first-degree or second-degree relatives with LS-related cancers, one of whom was diagnosed before age 50
    - 3 or more first-degree or second-degree relatives with LS-related cancers regardless of age
- An individual with a 5% risk or greater of having an MMR gene pathogenic variant based on predictive models (i.e., PREMM5, MMRpro, MMRpredict)
- An individual with a personal history of CRC and/or endometrial cancer with a PREMM5 score of 2.5% or greater.
- A personal history of mismatch repair deficiency in any solid tumor

Some individuals will have variants of uncertain significance (VUS); post-test counseling should include considering referral to research studies for the purpose of learning the functional impact of VUSs such as variant reclassification programs through clinical labs or registries (p. HRS-3 and EVAL-A 8 of 9).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

DEFINITIONS

1. **Adenomatous polyposis** are conditions that cause multiple adenomas (i.e., benign polyps) in the gastrointestinal tract.

2. **Breast cancer** is a term that applies to patients with invasive cancer or ductal carcinoma in situ (DCIS).

3. **Close relatives** include first, second, and third degree blood relatives:

    a. **First-degree relatives** are parents, siblings, and children

    b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings

c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

4. **Adjuvant treatment with olaparib therapy** may be indicated for cancer defined as

    a. Triple-negative breast cancer treated with either:

        i. Adjuvant chemotherapy with axillary node-positive disease or an invasive primary tumor greater than or equal to 2 cm on pathology analysis, **OR**

        ii. Neoadjuvant chemotherapy with residual invasive breast cancer in the breast or resected lymph nodes, **OR**

    b. Hormone receptor positive disease treated with either:

        i. Adjuvant chemotherapy with four or more positive pathologically confirmed lymph nodes, **OR**

        ii. Neoadjuvant chemotherapy which did not have a complete pathologic response, with a CPS+CG score [pre-treatment clinical (CS) and post-treatment pathological stage (PS), estrogen-receptor status (E) and grade (G)] of 3 or higher.

5. **High-risk prostate cancer** is defined by NCCN as an individual who has one or more of the following high-risk features, but does not meet criteria for very-high-risk features:
    a. cT3-cT4
    b. Grade Group 4 or 5
    a. PSA > 20ng/ml

6. **Juvenile polyps** are associated with Juvenile Polyposis Syndrome. These polyps are exophytic and eroded. They typically contain the following: marked edema and inflammation within the lamina propria, cystic glands filled with thick mucin, and some degree of smooth muscle proliferation.

7. **Lynch syndrome-related cancer** is defined as any of the following cancer types: colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma.

8. **Maori ancestry** describes individuals who are of indigenous New Zealand ethnic background.

9. **Very-high-risk prostate cancer** is defined by NCCN as an individual who has at least two of the following:
    a. cT3-cT4
    b. PSA >40 ng/mL
    a. Grade Group 4 or 5